Complete Summary

GUIDELINE TITLE

Guidelines on TaT1 (non-muscle invasive) bladder cancer.

BIBLIOGRAPHIC SOURCE(S)

Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Bohle A, Palou J. Guidelines on TaT1 (non-muscle invasive) bladder cancer. Arnhem, The Netherlands: European Association of Urology (EAU); 2008 Mar. 22 p. [82 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Stage TaT1 (non-muscle invasive) bladder cancer

GUIDELINE CATEGORY

Diagnosis
Management
Risk Assessment
Treatment

CLINICAL SPECIALTY

Oncology
Surgery
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To help urologists with the clinical decisions regarding management of TaT1 (non-muscle invasive) bladder cancer

TARGET POPULATION

Patients with TaT1 (non-muscle invasive) bladder cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Assessment

1. Tumor, node, metastasis (TNM) staging
2. Histologic grading (World Health Organization [WHO] system)
3. Assessment of risk of tumor progression or recurrence
4. Imaging studies: intravenous urography (IVU), computed tomography (CT), ultrasonography (US)
5. Cytology of voided urine or bladder washings
6. Determination of urinary molecular markers
7. Cystoscopy and fluorescence cystoscopy
8. Transurethral resection (TUR) or biopsy of bladder and prostatic urethra

Treatment/Management

1. TUR followed by immediate postoperative (same day) installation
2. Adjuvant intravesical chemotherapy (mitomycin C, epirubicin, or doxorubicin)
3. Adjuvant intravesical Bacillus Calmette-Guérin (BCG)
4. Cystectomy
5. Frequency of chemotherapy or BCG treatment
6. Frequency of follow-up

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of diagnostic tests
- Inter- and intra-operator variability assessing carcinoma in situ (CIS) and dysplasia, stage (Ta vs. T1) and grading of tumors
- Recurrence or progression rate
- Disease-free survival
- Morbidity and mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A structured literature search was carried out aiming to identify the relevant meta-analyses of randomized trials. Whenever possible, recommendations are based on meta-analyses. In case meta-analyses could not be identified, data from randomized clinical trials formed the basis for the recommendations. Recommendations were based on consensus of expert opinions only when scientific data was ambiguous or conflicting, or in areas where scientific data was lacking.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

1a Evidence obtained from meta-analysis of randomized trials

1b Evidence obtained from at least one randomized trial

2a Evidence obtained from one well-designed controlled study without randomization

2b Evidence obtained from at least one other type of well-designed quasi-experimental study

3 Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports

4 Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

- The first step in the European Association of Urology (EAU) guidelines procedure is to define the main topic.
- The second step is to establish a working group. The working groups comprise about 4-8 members, from several countries. Most of the working group members are academic urologists with a special interest in the topic. Specialists from other medical fields (radiotherapy, oncology, gynaecology, anaesthesiology etc.) are included as full members of the working groups as needed. In general, general practitioners or patient representatives are not part of the working groups. Each member is appointed for a four-year period, renewable once. A chairman leads each group.
- The third step is to collect and evaluate the underlying evidence from the published literature.
- The fourth step is to structure and present the information. All main recommendations are summarized in boxes and the strength of the recommendation is clearly marked in three grades (A-C), depending on the evidence source upon which the recommendation is based. Every possible effort is made to make the linkage between the level of evidence and grade of recommendation as transparent as possible.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendation

A. Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
B. Based on well-conducted clinical studies, but without randomized clinical trials
C. Made despite the absence of directly applicable clinical studies of good quality

COST ANALYSIS

Since the costs of a transurethral resection, anaesthesia and hospitalization in most countries exceed the cost of 8.5 times one adjuvant chemotherapy instillation, one immediate instillation of chemotherapy is considered to be cost-effective.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The Appraisal of Guidelines for Research and Evaluation (AGREE) instrument was used to analyse and assess a range of specific attributes contributing to the validity of a specific clinical guideline.

The AGREE instrument, to be used by two to four appraisers, was developed by the AGREE collaboration (www.agreecollaboration.org) using referenced sources for the evaluation of specific guidelines. (See the "Availability of Companion Documents" field for further methodology information).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the grade of recommendation (A-B) are provided at the end of the "Major Recommendations" field.

Recommendations for Primary Assessment of TaT1 Bladder Tumours

- Renal and bladder ultrasonography, intravenous urography (IVU) or computed tomography (CT) in selected cases (tumours located in the trigone). (**Grade of recommendation: B**)
- Cystoscopy with description of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended. (**Grade of recommendation: C)**
- Urine analysis
- Urine cytology
- Transurethral resection (TUR) in one piece for small tumours (less than 1 cm), including a part from the underlying bladder wall. (**Grade of recommendation: B**)
- TUR infractions (including muscle tissue) for larger tumours. (**Grade of recommendation: B**)
- Biopsies of abnormal-looking urothelium, biopsies from normal-looking mucosa when cytology is positive or when exophytic tumour is of non-papillary appearance. (**Grade of recommendation: C**)
- Biopsy of the prostatic urethra in the case of bladder neck tumour, when bladder CIS is present or suspected or when abnormalities of prostatic urethra are visible. (**Grade of recommendation: C**)
- A second TUR at 2-6 weeks after the initial resection when it was incomplete or when a high-grade or T1 tumour was detected. (**Grade of recommendation: B**)
- The pathological report should specify the grade, the depth of tumour invasion and whether the lamina propria and muscle are present in the specimen. (**Grade of recommendation: C**)

Predicting Recurrence and Progression in TaT1 Tumours

The tables below provide a patient's risk of recurrence and progression based on their most important clinical and tumour characteristics. Using these tables, the urologist can discuss with a patient his prognosis and offer different treatment options.

For providing treatment recommendations, the European Association of Urology (EAU) working group suggests using a three-tier system reflecting the European Organization for Research and Treatment of Cancer (EORTC) risk tables, which define low-, intermediate-, and high-risk groups for both recurrence and progression (see Tables below).

Table: Weighting Used to Calculate Recurrence and Progression Scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

CIS = carcinoma in situ

Table: Probability of Recurrence and Progression According to Total Score

Recurrence Score	Probability of Recurrence at 1 Year		Probability of Recurrence at 5 Years		Recurrence Risk Group
	%	(95% CI)	%	(95% CI)	
0	15	(10-19)	31	(24-37)	Low risk
1-4	24	(21-26)	46	(42-49)	Intermediate risk
5-9	38	(35-41)	62	(58-65)	
10-17	61	(55-67)	78	(73-84)	High risk
Progression Score	**Probability of Progression at 1 Year**		**Probability of Progression at 5 Years**		**Progression Risk Group**
	%	(95% CI)	%	(95% CI)	
0	0.2	(0-0.7)	0.8	(0-1.7)	Low risk
2-6	1	(0.4-1.6)	6	(5-8)	Intermediate risk
7-13	5	(4-7)	17	(14-20)	High risk
14-23	17	(10-24)	45	(35-55)	

Note: Electronic calculators for these Tables are available at http://www.eortc.be/tools/bladdercalculator/.

Recommendations for Intravesical Therapy

- The type of intravesical therapy is based on the risk groups as shown in the table above.
- In patients at low risk of tumour recurrence and progression, one immediate instillation of chemotherapy is strongly recommended as the complete adjuvant treatment. (**Grade of recommendation: A**)
- In patients at an intermediate or high risk of recurrence and an intermediate risk of progression, one immediate instillation of chemotherapy should be followed by further instillations of chemotherapy or a minimum of 1 year of Bacillus Calmette-Guérin (BCG). (**Grade of recommendation: A**)
- If chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug during instillation by reducing fluid intake. The optimal schedule and the duration of the chemotherapy instillations remain unclear, but it should probably be given for 6 to 12 months. (**Grade of recommendation: B**)
- In patients at high risk of tumour progression, intravesical BCG for at least 1 year. Immediate radical cystectomy may be offered to the highest risk patients. (**Grade of recommendation: A**)
- The absolute risks of recurrence and of progression do not always indicate the risk at which a certain therapy is optimal. The choice of therapy may be considered differently according to what risk is acceptable for the individual patient and the urologist.

Recommendations for Follow-Up Cystoscopy

- Patients with tumours at low risk of recurrence and progression should have a cystoscopy at 3 months. If negative, the following cystoscopy is advised at 9 months and consequently yearly for 5 years. (**Grade of recommendation: B**)
- Patients with tumours at high risk of progression should have a cystoscopy at 3 months. If negative, the following cystoscopies should be repeated every 3 months for a period of 2 years, every 4 months in the third year, every 6 months thereafter until 5 years, and yearly thereafter. A yearly exploration of the upper tract is recommended. (**Grade of recommendation: B**)
- Patients with intermediate-risk of progression (about one-third of all patients) should have an in-between follow-up scheme, adapted according to personal and subjective factors. (**Grade of recommendation: B**)

Definitions:

Grades of Recommendation

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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Early and successful treatment of bladder cancer confined to the mucosa or submucosa

POTENTIAL HARMS

- Severe complications have been reported in patients receiving intravesical chemotherapy in whom extravasation of the drug occurred. Thus, an immediate chemotherapy instillation should be omitted in case of overt or suspected intra- or extra-peritoneal perforation, which is most likely to appear in extensive transurethral resection (TUR) procedures.
- Assuming that maintenance therapy is necessary for optimal efficacy, the issue of Bacillus Calmette-Guérin (BCG) toxicity becomes more relevant. Compared to intravesical chemotherapy, BCG has more pronounced side-

effects. Deaths due to BCG sepsis and the high frequency of BCG-induced cystitis have been reported and compromised the use of BCG. However, with increased experience in applying BCG, the side-effects now appear to be less prominent. Serious side-effects are encountered in less than 5% of patients and can be effectively treated in virtually all cases. Major complications can appear after systemic absorption of the drug. Thus, BCG should not be administered during the first 2 weeks after transurethral resection, in patients with haematuria and after traumatic catheterization.

CONTRAINDICATIONS

CONTRAINDICATIONS

Severe complications have been reported in patients receiving intravesical chemotherapy in whom extravasation of the drug occurred. Thus, an immediate chemotherapy instillation should be omitted in case of overt or suspected intra- or extra-peritoneal perforation, which is most likely to appear in extensive transurethral resection (TUR) procedures.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The purpose of this text is not to be proscriptive in the way a clinician should treat a patient but rather to provide access to the best contemporaneous consensus view on the most appropriate management currently available. European Association of Urology (EAU) guidelines are not meant to be legal documents but are produced with the ultimate aim to help urologists with their day-to-day practice.
- The EAU believe that producing validated best practice in the field of urology is a very powerful and efficient tool in improving patient care. It is, however, the expertise of the clinician which should determine the needs of their patients. Individual patients may require individualized approaches which take into account all circumstances and treatment decisions often have to be made on a case-by-case basis.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Association of Urology (EAU) Guidelines long version (containing all 19 guidelines) is reprinted annually in one book. Each text is dated. This means that if the latest edition of the book is read, one will know that this is the most updated version available. The same text is also made available on a CD (with hyperlinks to PubMed for most references) and posted on the EAU websites Uroweb and Urosource (www.uroweb.org/professional-resources/guidelines/ & http://www.urosource.com/diseases/).

Condensed pocket versions, containing mainly flow-charts and summaries, are also printed annually. All these publications are distributed free of charge to all

(more than 10,000) members of the Association. Abridged versions of the guidelines are published in European Urology as original papers. Furthermore, many important websites list links to the relevant EAU guidelines sections on the association websites and all, or individual, guidelines have been translated to some 15 languages.

IMPLEMENTATION TOOLS

Pocket Guide/Reference Cards

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Mar

GUIDELINE DEVELOPER(S)

European Association of Urology - Medical Specialty Society

SOURCE(S) OF FUNDING

European Association of Urology

GUIDELINE COMMITTEE

Non-Muscle Invasive Bladder Cancer Guidelines Writing Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: M. Babjuk; W. Oosterlinck; R. Sylvester; E. Kaasinen; A. Böhle; J. Palou

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All members of the Non-Muscle Invasive Bladder Cancer guidelines writing panel have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology (EAU) Central Office database. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the European Association of Urology Web site.

Print copies: Available from the European Association of Urology, PO Box 30016, NL-6803, AA ARNHEM, The Netherlands.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- EAU guidelines office template. Arnhem, The Netherlands: European Association of Urology (EAU); 2007. 4 p.
- The European Association of Urology (EAU) guidelines methodology: a critical evaluation. Arnhem, The Netherlands: European Association of Urology (EAU); 18 p.

The following is also available:

- Guidelines on non-muscle invasive bladder cancer. 2008, Ultra short pocket guidelines. Arnhem, The Netherlands: European Association of Urology (EAU); 2008 Mar. 11 p.
- Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008 Aug;54(2):303-14.

Print copies: Available from the European Association of Urology, PO Box 30016, NL-6803, AA ARNHEM, The Netherlands.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on July 2, 2008. The information was verified by the guideline developer on August 29, 2008.

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